IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Maurice Israel et al.	Group Art Unit: 1623
Application No.: 10/051,243	Examiner: MCINTOSH III, TRAVISS C
Filed: January 22, 2002	Confirmation No.: 8007
For: METHODS FOR THE PREVENTION AND/OR THE TREATMENT OF GLUTAMATE CYTOTOXICITY)	

DECLARATION OF LAURA BOSSI, M.D.

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

- I, Laura Bossi, M.D., hereby state as follows:
- Since 2004 I have held the position of Chief Medical Officer of Faust Pharmaceuticals. Faust Pharmaceuticals has an interest in the above captioned patent application.
- 2. I am a neurologist and have been involved in neurological research and pharmaceutical development for neurological conditions for more than 30 years. I am a member of the American Academy of Neurology.
- 3. From 1993-1996, I was Vice-President of CNS Projects for SANOFI Recherche, Gentilly/Paris. From 1997 through 1999, I was Vice-President of the CNS Therapeutic Area for SANOFI Recherche, Gentilly/Paris, France with worldwide responsibility for the clinical development of the CNS portfolio. From 2000-2006, I was President, CEO and Founder of PHYSIS S.A.S., a company providing strategic consulting services in the area of biopharmaceuticals. From 2002-2007, I have held the position of President and co-founder of ELISTEM Biopharmaceuticals S.A.S., a biopharmaceutical start-up company focusing on the development of therapeutic proteins and peptides for disease-modifying treatment of neurodegenerative disorders.
 - 4. Copies of my curriculum vitae and bibliography are attached.

Ms

- 5. The following opinions are based upon my personal experience in the field of neurology and pharmacology. I understand that the subject patent application was first filed in 1999 and was filed internationally in 2000 and entered the U.S. as an application in 2002. Accordingly, I understand that the relevant time period for inquiries related to the state of the art at the time the subject patent application was filed is around 1999. Opinions expressed with regard to what would have been known or believed in the relevant time frame are believed to be consistent with the perspective of a person of ordinary skill in the field from 1999 to the present. I have also consulted with another eminent expert in the field who has provided an independent report that is entirely consistent with my opinions (see below).
- 6. I have read the above captioned patent application, the pending claims, and the remarks of the examiner concerning the rejection of claims 9, 10, and 12 in view of U.S. Patent Number 5,523,322 issued to Blache et al. and Lechner et al., *Wiener Medizinische Wochenschrift*, 136:387-91, 1986. I have reviewed the Blache and Lechner publications.
- 7. A person of ordinary skill in the field of the subject patent application in the relevant time frame would have been a person who had a doctorate degree in medicine, pharmacy or science (chemistry, biology, pharmacology...) and several years of research experience particularly related to the development of treatments for neurological disorders including Parkinson's disease.
- 8. Blache et al. describes a method of inhibiting blood platelet aggregation.

 Blache et al. would not have suggested a method of treating Parkinson's disease to a person of ordinary skill in the field.
- 9. Lechner et al. report results of a study on an atypical group of patients with a Parkinson's like disorder that appears to involve a vascular risk. The term "Lechner-Ott-Syndrome" is not found in the general literature on Parkinson's disease. Indeed, the cited article seems to stand alone. In my opinion, a person of ordinary skill in the art would not have considered the report by Lechner et al. in choosing a drug for treatment of Parkinson's disease, because the report of Lechner et al. concerns such an atypical group of patients and the observations of Lechner et al. were never repeated. To choose a drug for the treatment of Parkinson's disease on the basis of the Lechner et al. report would have been contrary to the



conventional wisdom in the field in 1999, and today, regarding the causes and consequences of Parkinson's disease.

- 10. For the reasons outlined below, I believe that a person of ordinary skill in the art from 1999 to the present would not have considered that Parkinson's disease is caused by vascular lesions, that there is significant vascular involvement in Parkinson's disease, or that an increased vascular risk profile is associated with Parkinson's disease. In particular, a person of ordinary skill in the art would not have considered platelet aggregation to be a factor in Parkinson's disease. Therefore, a person of ordinary skill in the art would not have considered any putative effects on platelet aggregation or other vascular effects in choosing an agent for use in a therapeutic composition for the treatment of Parkinson's disease.
- Parkinson's disease is not a vascular problem but a primary neurodegenerative disorder of unknown cause. See, e.g. Marsden, Lancet, April 21, 1990, pp. 948-52. Accepted wisdom in the art in the decade preceding the subject patent application was that "Research into Parkinson's disease in the next decade will centre on improvements in neuroprotective treatment to prevent or slow the rate of progression of the disease; methods of protection against free radical damage; the role of excitatory amino acid antagonists, and specific methods of delivery of such agents to the brain; and early diagnosis for the most effective use of neuroprotective agents." Id. at 951, 2nd paragraph.
- remains the 'gold standard' in the treatment of the disease...several neuroprotective drugs are now in development in experimental research..." Montastruc et al., Drugs and Aging, 9:169-84, 1996 at 169. Poewe et al. indicated that studies in the late 1990's were directed to the "...development of neuroprotective strategies that would modify the progression of disease.." Poewe et al., Ann Neurol., 44:S1-S9, 1998 at §1. The neuroprotective agents expected to give results according to Powe et al. were "...antioxidants including vitamine C, tocopherol and deprenyl, as well as antiglutamate agents including amantadine, dopamine agonists and neuronal growth factors" Id. at S5, §2. A good clinical review that predicted developments in Parkinson's disease from the time the application was filed in 1999 indicated



that "clinical trials of new drugs with neuroprotective and neurorescue properties are in progress." Schapira et al., British Medical Journal, 318:311-14, 1999.

- 13. Thus, throughout the 1990's levodopa therapy remained the treatment of choice for Parkinson's disease and research and development efforts were directed towards neuroprotective agents and novel dopaminergic drugs. The prevailing view did not consider vascular effects or platelet aggregation as a factor to consider in developing a treatment for Parkinson's disorder.
- 14. In considering the issues raised by the examiner in the subject patent application, I have consulted a colleague, Christopher G. Goetz, a world renowned neurologist and Parkinson's specialist who holds the positions of Professor of Neurological Sciences and Professor of Pharmacology at Rush University Medical Center, Chicago, Illinois, USA. Dr. Goetz is board certified as a neurologist (1981) from the American Board of Psychiatry and Neurology, and an active member of the American Academy of Neurology, the American Neurological Association, the French Neurological Society, and the Movement Disorder Society. He has been an active researcher in the fields of neurology and pharmacology for more than 30 years and has authored or co-authored more than 300 published scientific and medical journal articles.
- 15. Dr. Goetz prepared an expert report addressing several inquiries that I put to him. I have read his report and his opinions in the matters discussed in his report are entirely consistent with my own. A copy of Dr. Goetz's report is attached and is incorporated by reference herein in its entirety.
- 16. Dr. Goetz's analysis shows, and I agree, that Parkinson's disease and vascular parkinsonism are two distinct neurological conditions, and Parkinson's disease is not felt to relate to primary vascular pathology. In my opinion, this has been the prevailing view of persons of ordinary skill in the field throughout the time frame from 1999 to the present.
- 17. Dr. Goetz's analysis shows, and I agree, that in 1999 as in the present, a person of ordinary skill in the art would have recognized that the small body of evidence for vascular involvement in Parkinson's disease suggests only minor involvement and such involvement may be indirect. In the time frame from 1999 to the present, a person of ordinary skill in the



art would have considered that vascular involvement is not a significant part of Parkinson's disease.

- 18. Dr. Goetz's analysis shows, and I agree, that the evidence does not suggest that Parkinson's disease relates to a higher vascular risk profile. Indeed, the opposite may be the case. Therefore, I believe that a person of ordinary skill in the art in the time frame from 1999 to the present would not have considered vascular risk profile factors as relating to Parkinson's disease or that a diagnosis of Parkinson's disease implied an increased vascular risk.
- 19. Dr. Goetz's analysis shows, and I agree, that there has been no conclusive evidence that platelet aggregation is a factor in Parkinson's disease. Moreover, because of the atypical nature of the patients in the group reported by Lechner, and the apparent lack of any other reference to a Lechner-Ott syndrome in the literature of the field, it is my opinion that a person of ordinary skill in the art from 1999 to the present would not have looked to the Lechner report for guidance in developing a treatment for Parkinson's disease.
- 20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/10/67

Laura Bossi, M.D.

Attachments:

CV and Bibliography of Laura Bossi, M.D. Expert Report Prepared by Christopher G. Goetz, M.D.

V/B



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Harold L. Klawans, M.D. (1937-1998) - Founder

Christopher G. Goetz, M.D. United Parkinson Foundation Professor of Neurology

Dr. Laura Bossi Faust Pharmaceuticals

October 8, 2007

Dear Dr. Bossi,

I have been contacted by you with a request to address issues related to Parkinson's disease, vascular risk factors, evidence of platelet aggregation defects and evidence of prior therapeutic treatments affecting platelet aggregation in Parkinson's disease. It is my understanding that there are patent issues related to an agent with putative effects on platelet aggregation being developed for an indication of treatment for Parkinson's disease. Several questions have been posed to me and the main time frame of reference is 1999-2002.

I am a neurologist and hold the titles of Professor of Neurological Sciences and Professor of Pharmacology at Rush University Medical Center, Chicago, Illinois, USA. I am board certified as a neurologist (1981) from the American Board of Psychiatry and Neurology, and am an active member of the American Academy of Neurology, the American Neurological Association, the French Neurological Society, and the Movement Disorder Society. I serve as the Co-Editor-in-Chief of *Movement Disorders*, the primary international journal dealing with Parkinson's disease. I am the Editor of the major general neurology textbook, *Textbook of Clinical Neurology* (Saunders-Elsevier Publishers) now in its third edition (2007). I am involved in clinical research and have an active clinical practice that specializes in Parkinson's disease and related disorders. In the past, I directed neurological residency training at Rush University and also served on the MKSAP exam writing committee, so I am very aware of standard neurological knowledge and competency expectations for neurologists in the United States. For these reasons, I consider myself qualified to address the issues that have been posed to me. In the interest of disclosure, I have been a paid consultant by Faust to participate in a conference call to discuss a proposed clinical trial in the past, and I will invoice Faust for my time to prepare this document.

Is Parkinson's disease caused by vascular lesions: is there a distinction between Parkinson's disease and vascular parkinsonism? Parkinson's disease is a primary neurodegenerative disease of unknown cause. The primary anatomical lesion involves degeneration of dopaminergic cells that reside in the substantia nigra (midbrain). These cells have projections to the caudate nucleus and putatmen (striatum) and synthesize the neurochemical, dopamine. As such, the hallmarks of Parkinson's disease are: degeneration of the substantia nigra dopamine cells and striatal depletion of dopamine. Whereas the cause of this degeneration and selective dopaminergic cell loss is unknown, hypotheses have focused on oxidative stress, free radical toxicity, and protein aggregation abnormalities that lead to progressive cell loss and secondary dopamine striatal depletion.²

In contrast to Parkinson's disease, patients in the aging population can develop strokes and when the vascular damage occurs in the striatum or surrounding areas, parkinsonism can develop.^{3,4} This entity, termed "vascular parkinsonism" is distinct from Parkinson's disease and was clearly recognized in the period of interest (1999-2002).4 Vascular parkinsonism cases accounted for 3-6% of cases in one clinic series of patients referred for parkinsonism.³ Other series have higher rates, likely reflecting more specialized tertiary care centers.⁴ Among patients being evaluated for deep-seated strokes (lacunar strokes), 38% have signs of parkinsonism.³ Among subjects with vascular parkinsonism, older age, prominent gait impairment rather than tremor, predominant lower body signs, falls and instability, dementia, signs of pyramidal tract involvement, and poor response to levodopa are typical⁴, helping clinicians to distinguish cases from those with Parkinson's disease. Abnormal MR or CT scans showing evidence of strokes, a past history of clinical strokes that precede parkinsonism and vascular risk factors like hypertension, heart disease, diabetes, hyperlipidemia and smoking are significantly more common in vascular parkinsonism than Parkinson's disease. In another study of 60 patients referred for evaluation of Parkinson's disease, 16 (27%) had signs of cerebrovascular disease. Only one patient with typical signs of Parkinson's disease had evidence of vascular disease.⁵ This latter observation indicates that on very rare occasions, the differentiation between Parkinson's disease and vascular parkinsonism may be difficult, but in the large proportion of cases, the two syndromes are categorically distinct.⁶⁻⁸ The distinction is operationalized in the entry criteria for clinical trials of Parkinson's disease and in my experience participating in over 100 treatment protocols for Parkinson's disease patients, subjects with vascular parkinsonism are always excluded, because they are considered to have an entirely separate entity. In summary, Parkinson's disease and vascular parkinsonism are two distinct nosological categories among neurological diagnoses, and Parkinson's disease is not felt to relate to primary vascular pathology.

Is there any evidence for vascular involvement in Parkinson's disease? Whereas strokes causing vascular parkinsonism are altogether different from Parkinson's disease, there is a small body of evidence that implicates at least minor vascular involvement in Parkinson's disease. First, in some reports, hyperhomocysteinemia has been documented in Parkinson's disease patients, although the elevated levels may be related to levodopa treatment as opposed to the disease itself. Certain genotypes may be more likely to express hyperhomocysteinemia than others. Additionally, though controversial, some studies suggest that vascular amyloid-beta deposition occurs in Parkinson's disease. These issues are not settled, and their implications in terms of dopamine cellular degeneration, the hallmark of Parkinson's disease, is unknown. The seminal data pertinent to this area of science are all more recent than the period in question (1999-2002).

What is the vascular risk factor profile of patients with Parkinson's disease? Studies of risk factors for Parkinson's disease have consistently documented that a family history of Parkinson's disease, pesticide/herbicide exposure, and well-water drinking increase the risk of disease whereas tobacco use is a protective influence. In a study specifically examining risk factors for vascular disorders in Parkinson's disease patients, diabetes, smoking, hypertension, high blood glucose, high cholesterol and triglycerides were significantly less frequent in Parkinson's disease patient compared to controls. As early as 1990, epidemiological studies have documented a lower risk of stroke in patients with Parkinson's disease, and have hypothesized that this effect may be due to less tobacco use, decreases in generalized atheroschlerosis and dopamine deficiency. Whereas, these observations suggest that Parkinson's disease patients are actually protected against strokes, published studies and clinical experience clearly demonstrate that Parkinson's disease can develop stroke as a late co-morbidity. Older age is associated with increased risks of co-morbidities in Parkinson's disease, and when a stroke occurs, overall morbidity is higher compared to patients without added strokes.

<u>Does platelet aggregation occur as part of Parkinson's disease?</u> As a physician who has devoted his academic career to the study and treatment of Parkinson's disease, I am not aware of any large study assessing platelet aggregation abnormalities in Parkinson's disease. In a PUBMED search of

"Parkinson's disease" and "platelet aggregation" there were 15 "hits", but only three articles with any pertinence to the issue. Two of these are in English, and one in German. A 1991 letter to the Editor of Stroke reported that a small sample of 25 Parkinson's disease patients were compared to 25 age- and gender-matched controls for platelet aggregation.¹⁹ The authors found that platelet aggregation induced by adenosine diphosphate and epinephrine was significantly decreased in Parkinson's disease subjects, whereas collagen-induced aggregation did not differ between the two groups. They hypothesized that the lower incidence of stroke observed in Parkinson's disease patients may relate in part to this aggregation profile. 19 To my knowledge, this observation has not been replicated in a second or larger sample. A 1976 letter to the Editor of the British Medical Journal examined platelet aggregation in PD patients being treated with bromocriptine, a dopamine agonist, and found no drug-related effects on platelet aggregation. Data were not shown, but no indication of aggregation abnormalities prior to bromocriptine were described and bromocriptine did not change platelet aggregation profiles after 15 days of treatment.²⁰ Finally, the report by Lechner and Bertha described a group of parkinsonian patients with late disease onset, a high prevalence of diabetes mellitus, increased blood viscosity, enhanced platelet aggregation, abnormal electroencephalograms, and poor levodopa response.²¹ This clinical profile is atypical for Parkinson's disease because of the poor response to the gold standard treatment for the disease, levodopa. The authors named this syndrome as Lechner-Ott syndrome, an eponym I have never encountered in my career. In checking the index of my own textbook and five other general neurology texts, I do not find this designation listed. A PUBMED search for Lechner-Ott syndrome identifies only the Lechner article cited above. Although I can find no further references to this syndrome, the clinical description of these patients is distinct from Parkinson's disease and warrants a separate designation.

Among current treatments for Parkinson's disease, is anti-platelet aggregation generally used to treat PD? Since the 1980's, the treatment of Parkinson's disease remains anchored in replacement strategies for the lost dopamine that is the basis for the motor impairments of the disease. Levodopa, dopamine agonists, monoamine oxidase inhibitors, and catechol-O-methyltransferase inhibitors are the primary agents used. have been a consultant to pharmaceutical firms developing all of these classes of drugs, and in my experience of studying the pharmacological profiles of these agents, I have not seen data that used platelet aggregation as an index of anti-parkinsonian efficacy. In the laboratory, drugs with putative effects on Parkinson's disease are screened by their effects on animal models directly related to dopamine depletion. As a teacher and researcher, in 1999-2002, as today, I have never advised or heard other international colleagues discuss anti-platelet aggregation strategies for the treatment of Parkinson's disease.

In this context, however, data from 2007 raise the issue of whether cholesterol sub-types and statin exposure may be related to Parkinson's disease risk. These data represent very early observations that need to be confirmed, but are pertinent to the issue of platelet aggregation. In one report, lower lowdensity lipoprotein cholesterol levels were associated with a higher occurrence of Parkinson's disease.²³ Further, cholesterol-lowering drugs or statins were associated with a lower occurrence of PD. A second study documented that statin effects may be drug-selective and not cross the entire class of agents, with chronic simvastatin and atorvastatin use associated with a reduced incidence of Parkinson's disease.²⁴ The biochemistry of statin drugs is complex, and includes stabilization of atherosclerotic plaques, decreased carotid intimal-medial thickness, protective effects agains nitric oxide synthase, antiinflammatory effects, and possible regulation of dopamine receptors. 25,26 There is however some evidence that these agents may affect platelet function as well, and both lovastatin and fluvastatin have been shown to reduce platelet aggregation.²⁷ Therefore, if the epidemiological observations are replicated and statin use is truly associated with a lower risk of Parkinson's disease, it is reasonable to consider that one possible mechanism is decreased platelet aggregation. These data examine risk for Parkinson's disease and not therapy for Parkinson's disease, but, in my view, the two issues may potentially be linked and therefore therapeutically relevant. I emphasize the preliminary nature of these data and the inability to make sound conclusions regarding platelet aggregation strategies relative to Parkinson's disease at the present time.

Is the structure of the compound described by Blache et al (US Patent number 5,523,322) similar to that of drugs used to treat Parkinson's disease? I am not a structural chemist, but as a Professor of Pharamcology, I have examined the structure of the compound in the Blache et al patent application and do not recognize similarities to any agent used for treating Parkinson's disease in 1999 or since then.

During the period 1999-2002, would a "person of ordinary skill", defined as a person with a doctorate degree in medicine or science and several years of research experience particularly related to the development of treatments for Parkinson's disease, have considered drugs with effects on platelet aggregation to have a therapeutic role in Parkinson's disease patients?

In the period of 1999-2002, I was Professor of Neurological Sciences and Professor Pharmacology at Rush University Medical Center. As an active teacher, researcher and member of the Movement Disorder Society, the American Neurological Association and the American Academy of Neurology, I was very well aware of the standard knowledge base of the group of colleagues you term "persons of ordinary skill". As an active member of that group, during the period 1999-2002, I can comfortably attest that "persons of ordinary skill" did not consider platelet aggregation disorders to be a factor in the causation or progressive disability of Parkinson's disease. At that time, and since then, "persons of ordinary skill" did not select agents for treating Parkinson's disease based on primary anti-platelet action.

Conclusions

- Parkinson's disease and vascular parkinsonism are different diagnoses.
- Parkinson's disease patients have a low risk for stroke, but late strokes can occur, especially in old patients. When strokes superimpose on Parkinson's disease, patients endure increased morbidity.
- In Parkinson's disease, there is a small set of data that raise the possibility of vascular involvement (hyperhomocysteinemia and increased vascular amyloid-beta deposition), but typical risk factors for vascular disease are less often seen in Parkinson's disease patients than the general population.
- No large studies demonstrate platelet aggregation alterations in Parkinson's disease. One small study suggested that Parkinson's disease patients have reduced platelet aggregation.
- The Lechner-Ott syndrome is clinically distinct from Parkinson's disease because of its lack of levodopa responsivity. Though the authors described increased platelet aggregation, they designated a special eponym for this distinct group of patients. The Lechner-Ott syndrome is not a regularly recognized term within the standard neurological nosology.
- Treatment for Parkinson's disease is anchored in dopaminergic pharmacology and no agent with a primary activity on platelet aggregation has been developed for Parkinson's disease.
- In 1999-2002, "persons of ordinary skill" (defined above) did not consider anti-platelet aggregation drugs as treatment for parkinsonism in Parkinson's disease. Furthermore, at that time, and since then, "persons of ordinary skill" have not selected agents for treating Parkinson's disease based on primary anti-platelet action.

Sincerely,

Christopher G. Goetz, M.D.

Professor of Neurological Sciences

Professor of Pharmacology

References

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CURRICULUM VITAE

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Languages: English, French, German, Italian (fluent - speaking, reading, writing); Spanish

(speaking, reading)

EDUCATION

C.
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DEGREES AND CERTIFICATIONS

1979	Specialist in Neurology (cum laude), Milan University
	Thesis: Possible role of the serotoninergic system in the pathogenesis of
	myoclonus.
1977	Specialist in Pharmacological Research, Istituto Mario Negri, Milan
1976	E.C.F.M.G. Certificate (Educational Commission for Foreign Medical
	Graduates, USA)
1975	Medical Degree (cum laude), Milan University
	Thesis: Treatment of epilepsy in childhood - results of two years of
	pharmacological and clinical monitoring.
1969	Abitur (Naturwissenschaftlicher Zweig), German School, Milan
	Maturità Scientifica, Liceo Vittorio Veneto, Milan

COMPLEMENTARY TRAINING

1994	La gestion chez SANOFI Recherche (residential training in finance and
	accounting)
1992	Management Center Europe: The Management Forum - Europe 2000 (Berlin)
1991	Management Center Europe: Advanced fundamentals of finance (Brussels)
1990	SDA Bocconi, Milan: Corso interno di formazione dei dirigenti FIDIA
	(residential advanced management training, Arcugnano, 1 month)
1988	Crown Eagle communication: Licensing (London)

1988 Management Center Europe: Marketing through distributors (Brussels)
1987 Management Center Europe: Fundamentals of finance and accounting for nonfinancial managers (Paris)

PROFESSIONAL SOCIETIES

American Academy of Neurology Italian Neurology Society French Neuroscience Society International Society for Biological Psychiatry International Society for the History of Neurosciences

Founding member of the French Foundation for Biological Psychiatry "Fondation Pierre Deniker"

AWARDS

1985	XVI Epilepsy International Symposium, Hamburg, 1984 Clinical
	Pharmacology Award
1979	XI Epilepsy International Symposium, Florence, Award for Research on
	Epilepsy

POSITIONS IN THE PHARMACEUTICAL INDUSTRY

Since 5/2004	Chief Medical Officer of FAUST Pharmaceuticals, a clinical stage	
	biopharmaceutical Company focusing on the discovery and development of	
	new therapies for CNS disorders and a spin-off of France's largest research	
	institution, the CNRS (see www.faustpharma.com)	

Since 4/2002	President and co-founder of ELISTEM Biopharmaceuticals S.A.S., a
	biopharmaceutical start-up Company focusing on the development of
	therapeutic proteins and peptides for disease-modifying treatment of
	neurodegenerative disorders. Main scientific founder: Alain Prochiantz,
	director of the department of Biology of the École Normale Supérieure, Paris

2000-2006 President, CEO and Founder of PHYSIS S.A.S., a company providing strategic consulting services in the area of biopharmaceuticals (main clients SANOFI-SYNTHELABO Group, UCB Pharma Corporate, Servier, Associés en Conseil, Tenec, Paris Biotech, biotech and biopharmaceutical start-up companies, Venture Capital societies).

1997- 12/1999Vice-President, CNS Therapeutic Area, SANOFI Recherche, Gentilly/Paris, France.

Worldwide responsibility for the clinical development of the CNS portfolio (phases IIa-IIIb).

Clinical programs on 10 compounds:

Phase IIIb: Depakine® - Depakote® (mania), Tiagabine® (epilepsy) Phase III: Xaliprodene, a non-peptidic neurotrophic compound (ALS)

Phase IIb: rimonibant, a cannabis CB1 antagonist in obesity/eating disorders; a 5HT2 antagonist in sleep disorders

Phase IIa: five compounds in schizophrenia (a 5-HT2 antagonist, a sigma ligand, a neurotensin antagonist, a cannabis CB1 antagonist, a neurokinin 3 antagonist); four compounds in major depressive disorders (a beta-3 agonist, a 5-HT2 antagonist, a neurokinin 3 antagonist and a neurokinin 2 antagonist); a non-peptidic neurotrophic compound in dementia (Alzheimer)

Exploratory programs: anxiety disorders, substance abuse, movement disorders, pharmaco-EEG, brain imaging.

Preparation of a NDA (neurotrophic compound – xaliprodene - in ALS). Number of clinical studies conducted in 1999: 38 trials on 8 compounds; 26 new studies launched.

Direct management of a team of 8 Clinical Research Directors, 6 MDs and 2 PhDs, based in France (5) and in the US (3). Management of an operational team (France-US) of ca 40 people. Coordination of clinical research & operations in the CNS therapeutic area (corporate & clinical research units in the affiliates – ca 200 people). Coordination of subcontracting to various international CROs.

- Vice-President, CNS Projects, SANOFI Recherche, Gentilly/Paris
 Reporting directly to Gérard Le Fur. Responsible for the preclinical, industrial, regulatory, clinical & strategic marketing development (worldwide) of 14 compounds in the areas of schizophrenia, mood disorders (MDD, bipolar disorders), anxiety disorders, epilepsy, ALS, dementia, sleep disorders, substance abuse, eating disorders, movement disorders.

 Coordination of 14 project teams, each including ca 20 specialists (European & US) of all professional areas from preclinical research to marketing. INDs obtained for 6 compounds.
- President and General Manager, Fidia Farmacéutica, Madrid, Spain Incorporation, organization and management of the Spanish subsidiary of Fidia.

 Main missions: to represent the headquarters in the contacts with regulatory authorities in Spain and Portugal, licensees, and production facilities; clinical research in Spain and Portugal, directly or via CROs; harmonization of marketing strategy of licensees; institutional communication
- 1986-1993 President and General Manager, Fidia France, Paris
 Incorporation, organization and management of the French subsidiary of Fidia.
 Main missions: preclinical and clinical development, regulatory affairs, outlicensing, marketing strategy (in collaboration with licensees), institutional communication.
 Clinical Development (5 compounds) & Regulatory Affairs in the areas of peripheral neuropathies, dementia, stroke, spinal cord injury, osteoarthritis, ocular surgery (European French Speaking Countries, UK, Spain and Portugal).

Marketing approval obtained for Hyal® - Ialum® in ocular surgery (Luxemburg 1991, France 1992, Belgium 1992) and Hyalgan® in osteoarthritis (France 1991, Luxemburg 1992, Belgium 1993).

Preclinical research in the area of neuroplasticity in collaboration with academic research laboratories.

1982-1986 Associated Head, then (1984) Head of the CNS group, Clinical Research Department, LERS (Laboratoires d'Études et de Recherches Synthélabo), Paris Worldwide clinical development of the CNS portfolio - in the areas of epilepsy, movement disorders, depression, sleep disorders, stroke (phases I-III) Main projects: Progabide (Gabrene®), Zolpidem (Stilnox®), alpidem, ifenprodil (Vadilex®) and back-up compounds Marketing approval obtained for Progabide (Gabrene®) in epilepsy (France,

1985)

Preclinical and clinical research collaborations on the role of the GABA-ergic system in epilepsy, mood disorders, movement disorders.

1979-1982 Project leader, CNS international projects, Clinical Research Department, LERS-Synthélabo, Paris, France

> Responsible for the clinical development of the CNS portfolio in all countries except France.

Main project: Progabide.

Preclinical and clinical research collaborations on the role of the GABA-ergic system in epilepsy, mood disorders and movement disorders.

RESEARCH POSITIONS

1979-1982 Research Associate, Epilepsy Research Unit 97, INSERM, Paris, France (Dr. Bancaud, Dr. Tailarach) Semiology of epileptic seizures and localization of the epileptogenic area. Brain concentrations of anticonvulsants, GABA, and other neurotransmitters in epileptic patients undergoing brain surgery (cortectomy).

1977-1978 Research Associate, Clinical Pharmacology Laboratory, Mario Negri Institute, Milan, Italy (Prof. Garattini, Dr. Morselli) Clinical pharmacology and pharmacokinetics of antiepileptic drugs. Role of the serotonergic system in myoclonus. Coordination of a collaborative program (Milan - Berlin, Prof. Janz) on epilepsy, pregnancy, and the child.

1976-1977 Fellow, Research Training Program of the Italian National Research Council (CNR), Mario Negri Institute, Milan, Italy (Prof. Garattini) Clinical pharmacology of antiepileptic drugs.

BOOKS

- 1. Epilepsy, pregnancy and the child. Edited by D. Janz, L. Bossi, M. Dam, H. Helge, A. Richens and D. Schmidt. Raven Press, New York, 1982.
- 2. Epilepsy and GABA Receptor Agonists, Basic and Therapeutic Research. L.E.R.S. Monograph series: Volume 3.

Edited by G. Bartholini, L. Bossi, K.G. Lloyd and P.L. Morselli. Raven Press, New York, 1985.

3. Histoire naturelle de l'âme.

Laura Bossi

Presses Universities de France, Paris, 2003

4. Scoria naturale dell'anima.

Laura Bossi

Baldini e Castoldi, Milano, 2004

5. Historia natural del alma

Laura Bossi

Antonio Machado Libros, Madrid, 2007 (in press)

BOOKS/TRANSLATIONS

1. Il naso di Giacometti.

Jean Clair.

Translation Laura Bossi.

Donzelli, Roma, 1994

EXHIBITS

1. « Les Siècles d'Or de la Médecine »

Paris - Muséum d'Histoire Naturelle

24 May-18 December 1989 (producer)

Catalogue: Electa, Milan 1989; curator: Yves Hersant

The exhibit was followed by a series of conferences on the history of anatomy.

2. « Ramon y Cajal »

Madrid, Colegio de Medicos

1990 (producer, president of the scientific committee)

The exhibit was followed by an International Symposium, « Santiago Ramon y Cajal – past, present and future », and a series of conferences on the interaction between the neurosciences and creative art work, « El cerebro et si mismo », chaired by L. Bossi and A. Portera-Sanchez

3. « La Fabrique de la Pensée - La découverte du cerveau de l'art de la mémoire aux neurosciences »

Paris - Cité des Sciences, La Villette

18 April 1990 - 6 January 1991

(Producer, member of scientific committee)

Catalogue: Electa, Milano 1990; curator: Pietro Corsi

The exhibit was followed by a series of conferences on the neurosciences.

4. « El Cerebro - del arte de la memoria a la neurociencia » Madrid - Museo Nacional de Ciencias Naturales, Madrid 14 November 1991-28 February 28 1992 (Producer, member of scientific committee)

5. « L'âme au corps »

Paris - Grand Palais

19 October 1993 - February 1993

(Author of an article published in the catalogue : L. BOSSI, L'âme électrique)

Catalogue: Gallimard – Editions des Musées de France, Paris 1993

Curator: Jean Clair

6. « Chimères »

Montecarlo, summer 2003

(Author of an article published in the catalogue: L. BOSSI, Les chimères existent-elles?)

Curator: Didier Ottinger

7. « Mélancolie. Génie et folie en Occident »

Paris, Grand Palais, 10 October 2005 – 16 January 2006

(Author of an article published in the catalogue: L. BOSSI, Mélancolie et

dégénérescence)

Catalogue: Gallimard – Editions de la Réunion des Musées Nationaux, Paris 2005

Curator & editor: Jean Clair

8. « Melancholie. Genie und Wahnsinn in der Kunst ».

Berlin, Neue Nationalgalerie, 17 February – 7 May 2006

(Author of an article published in the catalogue: L. BOSSI, Melancholie und

Entartung)

Catalogue: Hatje Cantz Verlag, Ostfildern-Ruit - Editions de la Réunion des Musées

Nationaux, Paris, 2006

Curator & editor: Jean Clair

PAPERS

Author of ca 100 full papers and numerous abstracts on neuropsychopharmacology, epileptology, therapeutics, and the history of neurosciences.

The full list of publications is available upon request.

LAURA BOSSI - Bibliography

FULL PAPERS

(in journals and books)

<u>1975</u>

1. BARUZZI A., **BOSSI L.**, CASTELLI D., GERNA M., RIGHETTI A., MORSELLI P.L.

Alcune considerazioni sulla farmacocinetica dei farmaci anticonvulsivanti nell'età evolutiva.

Gaslini 7: 125-130, 1975

2. FARGHALI-HASSAN, **BOSSI** L., ASSAEL B.M., MORSELLI P.L.

Placental transfer of carbamazepine in the rat.

J. Pharm. Pharmacol. 27: 956-957, 1975

3. VIANI F., **BOSSI L.**, GERNA M., MORSELLI P.L.

Indicazioni del monitoraggio dei livelli plasmatici dei farmaci antiepilettici.

Gaslini 7: 121-124, 1975

<u> 1976</u>

4. AVANZINI G., FRANCESCHETTI S., BARUZZI A., BORDO B., **BOSSI** L., MORSELLI P.L., PORRO M.G., ZAGNONI P., CANGER R., PRUNERI C., VIANI F. (Gruppo Milanese per lo studio delle Epilessie)

Problemi terapeutici nell'epilessia con crisi parziali : considerazioni su una esperienza di monitoraggio a lungo termine clinico-farmacologico.

Lega Italiana contro l'Epilessia. Bollettino 15/16: 37-45, 1976

5. BARUZZI A., BORDO B., **BOSSI** L., CASTELLI D., GERNA M., PORRO M.G., RIGHETTI A., SOFFIENTINI M.E., ZAGNONI P., MORSELLI P. L., AVANZINI G., BRESCHI F., FRANCESCHETTI S., CANGER R., DE CASTRO R., PRUNERI C., PIGNATELLI G., SMIRNE R., VIANI F. (Gruppo Milanese per lo studio delle Epilessie)

Monitoraggio intensivo dei farmaci antiepilettici : risultati generali di un'osservazione durata due anni.

Lega Italiana contro l'Epilessia, Bolletino 15/16 : 27-36, 1976

6. BARUZZI A., **BOSSI L**., MORSELLI P.L.

Concentrazioni plasmatiche di di-n-propilacetato e clonazepam nei pazienti epilettici. In : Atti des Convegno della Società Italiana di Neuropsichiatria Infantile. Le epilepssie miocloniche in età evolutiva, Giovanardi Rossi P., ed., Bologna, pp. 49-62, 1976

7. **BOSSI L.**, BARUZZI A., PORRO M.G.

Terapia antiepilettica in gravidanza: valutazione rischi-benefici.

Lega Italiana contro l'Epilessia, Bollettino 15/16: 89-104, 1976

8. FARGHALI-HASSAN, ASSAEL B.M., **BOSSI L.**, GARATTINI S., GERNA M., GOMENI R., MORSELLI P.L.

Carbamazepine pharmacokinetics in young, adult and pregnant rats. Relation to pharmacological effects.

Arch. Int. Pharmacodyn. Ther. 220: 125-139, 1976

9. MORSELLI P. L., **BOSSI L.**, GERNA M.

Pharmacokinetic studies with carbamazepine in epileptic patients.

In : Epileptic seizures, behaviour and pain. Birkmayer W., Ed., Hans Huber Publi., Berne, Stuttgart. Vienna, pp. 141-150, 1976

10. PAZZAGLIA P., AMBROSETTO G., FORTI A., SACQUEGNA T., LUGARESI E., BARUZZI A., **BOSSI** L., PORRO M.G., ZAGNONI P.

Il trattamento delle crisi epilettiche parziali con il phenobarbital, la difenilidantoina e la carbamazepina : studio longitudinale (4-22 mesi) guidato dalla determinazione dei livelli plasmatici.

Lega Italiana contro l'Epilessia, Bollettino 15/16 : 55-64, 1976

11. TOGNONI G., BARUZZI A., **BOSSI L.**, ZAGNONI P.

Sperimentazione clinica o critica della pratica medica?

In: Atti des simposio della Società Italiana di Neuropsicofarmacologica, A. Marino e D. de Maio e D. de Maio, Eds., Anacapri, Giugno 1976, pp. 61-69

12. VIANI F., RIBOLDI A., ROSSOTTI V., BARUZZI A., **BOSSI** L., CASTELLI D., MORSELLI P. L., SOFFIENTINI M.E., ZAGNONI P., AVANZINI G., FRANCESCHETTI S., CANGER R. (Gruppo Milanese per lo studio delle Epilessie) Monitoraggio a lungo termine dei farmaci antiepilettici : risultati in pazienti con sindrome di Lennox-Gastaut

Lega Italiana contro l'Epilessia, Bollettino 15/16: 47-54, 1976

1977

13. AVANZINI G., BARUZZI A., BORDO B., **BOSSI L.**, BRESCHI F., CANGER R., DE CASTRO R., FRANCESCHETTI S., GERNA M., MORSELLI P. L., PIGNATELLI G., PRUNERI C., SMIRNE S., VIANI F., ZAGONI P. (Milan Collaborative Group for Studies on Epilepsy)

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15. **BOSSI L., MORSELLI P. L.**

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- 16. MORSELLI P. L., BARUZZI A., GERNA M., BOSSI L., PORTA M. Carbamazepine and carbamazepine-10, 11-epoxide concentrations in human brain. Br. J. Clin. Pharmacol., 4: 535-540, 1977
- 17. VIANI F., AVANZINI G., BARUZZI A., BORDO B., **BOSSI** L., CANGER R., PORRO M.G., RIBOLDI A., SOFFIENTINI M.E., ZAGNONI P., MORSELLI P. L. (Milan Collaborative Group for studies in Epilepsy)

 Long term monitoring of antiepileptic drugs in patients with Lennox-Gastaut syndrome. In: **Epilepsy, The Eight International Symposium**, Penry J.K., Ed., Raven Press, N.Y., pp. 131-138, 1977

<u> 1978</u>

18. **BOSSI L.**

Anticonvulsivanti e psicofarmaci.

In: **Farmaci e gravidanza**, Mancini M., Tognoni G., Eds., Il Pensiero Scientifico, Roma, Anno XIV, N° 4, pp. 75-85, 1978

 CANGER R., SPINA S., ALTAMURA C., BOSSI L., PORRO M.G., SPAGNOLI A., COMO L., DE GIAMBATTISTA M., PARDI G., PIFAROTTI G., SPREAFICO R. Livelli plasmatici dei farmaci antiepilettici in corso di gravidanza (risultati preliminari). Lega Italiana contro l'Epilessia, Bollettino 22/23: 267-272, 1978

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20. AVANZINI G., **BOSSI L**., CARACENI T., CONSOLAZIONE A., FRANCESCHETTI S.

Possibli implicazioni del sistema serotoninergico nella patogenesi delle mioclonie. Dati preliminari di uno studio clinico.

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English abstract:

Possible role of the serotoninergic system in the pathogenesis of myoclonus. Preliminary data of a clinical trial.

EEG Clin. Neurophysiol. 1981, p. 76

21. **BOSSI L.**

Effetti indesiderati dei farmaci antiepilettici : review della letteratura.

Lega Italiana contro l'Epilessia, Bollettino 25/26 : 5-29, 1979

22. **BOSSI** L., AVANZINI G., BATTINO D., CANGER R., CROCI D., FRANCESCHETTI S., PORRO M.G., PRUNERI C., SPINA S., SPREAFICO R.

Monitorage des médicaments antiépileptiques pendant la grossesse. Signification clinique des modifications des niveaux plasmatiques des médicaments antiépileptiques. Expériences chez 30 malades.

Lyon Médical, 242: 597-603, 1979

23. **BOSSI L., PORRO M.G., TOGNONI G.**

Farmaci antiepilettici e psicofarmaci in gravidanza.

Rivista degli Ospedali. 11 : 271-281, 1979

24. FRANCESCHETTI S., BOSSI L., CEFALA A., AVANZINI G.

Criteri elettrofisiologici di classificazione del mioclono: studio di 16 casi

Riv. Ital. EEG Neurofisiol. Clin., 3:17-20, 1979

English abstract:

Electrophysiological classification criteria for myoclonus. Study of 16 cases.

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25. AVANZINI G., **BOSSI L.**, CARACENI T., CONSOLAZIONE A., FRANCESCHETTI S., NEGRI S., PARATI E.

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26. AVANZINI G., FRANCESCHETTI S., CEFALA A., BOSSI L., ROVEI V.

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27. BATTINO D., **BOSSI** L., CROCI D., FRANCESCHETTI S., GOMENI C., MOISE A., VITALI A

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Therapeutic Drug Monitoring, 2: 315-322, 1980

28. BATTINO D., MOLTENI B. SPINA S., **BOSSI L**., CANGER R., MARGSTAKLER E., ROSSI E.

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29. **BOSSI** L., ASSAEL B.M., AVANZINI G., BATTINO D., CACCAMO M. L., CANGER R., COMO M.L., PIFAROTTI G., DE GIAMBATTISTA M., FRANCESCHETTI S., MARINI A., PARDI G., PORRO M.G., ROVEI V., SANJUAN M., SOFFIENTINI M.E., SPINA S., SPREAFICO R.

Plasma levels and clinical effects of antiepileptic drugs in pregnant epileptic patients and their newborns.

In: Antiepileptic therapy - Advances in drug monitoring, Johannessen S.L., Morselli P.L., Pippenger C.E., Richens A., Schmidt D., Meinardi H., Eds., Raven Press, N.Y., pp. 9-14, 1980

30. **BOSSI L.,** ASSAEL B.M., AVANZINI G., BATTINO D., CACCAMO M.L., CANGER R., COMO M.L., PIFAROTTI G., DE GIAMBATTISTA M., FRANCESCHETTI S., MARINI A., PARDI G., PORRO M.G., ROVEI V., SANJUAN M., SOFFIENTINI M.E., SPINA S., SPREAFICO R.

Plasma level and clinical effects of antiepileptic drugs in pregnant epileptic patients and their newborns.

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31. **BOSSI** L., AVANZINI G., BATTINO D., CANGER R., COMO M.L., CROCI D., DE GIAMBATTISTA M., FRANCESCHETTI S., PIFAROTTI G., PORRO M.G., PRUNERI C., SPINA S., SPREAFICO R.

Plasmaspiegelbestimmungen während der Schwangerschaft : Klinische Bedeutung von Änderungen des Plasmaspiegel.

In: **Epilepsie 1979**, Doose H., M., Gross-Selbeck G., Meinardi H., Eds., Georg Thieme Verlag, Stuttgart, pp. 16-22, 1980

32. **BOSSI** L., BATTINO D., CACCAMO M.L., CANGER R., COMO M.L., DE GIAMBATTISTA M., MARINI A., PARDI G., PIFAROTTI G., PORRO M.G., ROVEI V., SANJUAN M., SERENI F.

Klinische und pharmakologische Beobachtungen bei 31 Neugeborenen von epileptischen Müttern.

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33. CANGER R., AVANZINI G., BATTINO D., **BOSSI** L., COMO M.L., CROCI D., DE GIAMBATTISTA M., FRANCESCHETTI S., PARDI G., PIFAROTTI G., PRUNERI C., SPINA S., SPREAFICO R., STERZI R.

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34. MORSELLI P.L., BARUZZI A., **BOSSI L**., AVANZINI G., FRANCESCHETTI S., CANGER R., VIANI F.

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35. MORSELLI P.L., BOSSI L.

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1981

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- 49. SEMERDJIAN-ROUQUIER L., BOSSI L., SCATTON B.

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1982

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Abstracts, p. 196

BATTINO D., BRESCHI F., **BOSSI** L., CROCI D., FRANCESCHETTI S., MOISE A. Carbamazepine plasma levels in children (poster) Abstracts, p. 179

BEGHI E., **BOSSI** L., PORRO M.G., SASANELLI F., SPAGNOLIA A., TOGNONI G. Diagnosis and treatment of epileptic patients in hospital practice in Lombardy Abstracts, p. 183

FRANCESCHETTI S., **BOSSI** L., CEFALA A., AVANZINI G. Clinical and neurophysiological evaluation of the effects of L-5HTP on myoclonus Abstracts, p. 139

BATTINO D., **BOSSI** L., CROCI D., CUSI C., GOMENI C., MOISE A., SPINA S. Plasma levels of primidone and phenobarbital in children and adults: influence of age and associated therapy

MYRTLE BEACH (U.S.A.) - 6-10 November 1979

International Symposium on GABA and other inhibitory neurotransmitters MORSELLI P.L., **BOSSI** L., HENRY J.F., ZARIFIAN E., BARTHOLINI G. Preliminary observations on the action of SL 76002, a new GABA-mimetic compound, in neuropsychiatric disorders

Abstract : Brain Res. Bull. 4 : 692, 1979

<u>1980</u>

AIX EN PROVENCE - 11-15 May 1980

IIème Réunion commune des Ligues espagnoles, italienne et française contre l'épilepsie BATTINO D., **BOSSI L.**, MARGSTALKER E., MOLTENI B., ROSSI E., SPINA S. Modificazioni del sistema emostatico in neonati da madre epilettiche in terapia cronica. Risultati preliminari.

PORTO CERVO (CAGLIARI) - May 1980

International Symposium on GABA and glutamate as neurotransmitters LLOYD K.G., MUNARI C., WORMS P., **BOSSI L.**, BANCAUD J., TALAIRACH J., MORSELLI P.L.

The role of GABA mediated neurotransmission in convulsive states.

GOTEBORG (SUEDE) - 21-22 June 1980

Neuropsychopharmacologia, International Meeting

LLOYD K.G., MUNARI C., **BOSSI** L., BANCAUD J., TALAIRACH J., MORSELLI P.L. Function and dysfunction of the GABA system in the human brain.

COLMAR (STRASBOURG) - 10-11 July 1980

XXVIIIth International Congress of Physiological Sciences, « Amino Acid Transmitters » LLOYD K.G., WORMS P., **BOSSI L.**, HENRY J.F., MORSELLI P.L.

Neuropharmacological actions of GABA agonists: predictability of their clinical usefulness Abstract

COPENHAGEN - 6-10 September 1980

XIIth Epilepsy International Symposium:

LLOYD K.G., WORMS P., BOSSI L., MORSELLI P.L.

GABA agonists: predictability for clinical usefulness by their neuropharmacological spectrum.

Abstract, Acta Neurol. Scand. Suppl. 79, 62:6, 1980

LOISEAU P., BOSSI L., CENRAUD B., MORSELLI P.L.

A double-blind controlled study versus placebo with Progabide (SL 76002) in severe epilepsy Abstracts, Acta Neurol. Scand. Suppl. 79, 62: 20-21, 1980

VAN DER LINDEN G.J., MEINARDI H., MEIJER J.W.A., BOSSI L., GOMENI C.

A double-blind cross-over trial with SL 76002 against placebo in patients with secondary generalized epilepsy.

Abstracts, Acta Neurol. Scand. Suppl. 79, 62:21, 1980

STOFFELS C., MUNARI C., BOSSI L., BONIS A., BANCAUD J., TALAIRACH J.

A stereo-EEG study of epileptic seizures with genital and sexual symptomatology Abstracts, Acta Neurol. Scand. Suppl. 79, 62: 95, 1980

MUNARI C., BONIS A., STOFFELS C., BOSSI L., TALAIRACH J., BANCAUD J.

Automatic activities during frontal and temporal lobe seizures: are they the same? Abstracts, Acta Neurol. Scand. Suppl. 79, 62: 101, 1980

BATTINO D, AVANZINI G., **BOSSI** L., CROCI D., CUSI C., GOMENI C., MOISE A., SPINA S.

Primidone and derived phenobarbital plasma concentrations in children (poster).

Abstracts, Acta Neurol. Scand. Suppl. 79, 62: 101, 1980

BERLIN - 14-16 September 1980 (member of Scientific Committee, chairperson)

1st Workshop on Epilepsy, pregnancy and the child (sponsored by Epilepsy International):

CANGER R., AVANZINI G., BATTINO D., BOSSI L., FRANCESCHETTI S., SPINA F.

Modification of seizure frequency in pregnant patients with epilepsy: a prospective study.

Abstract : Epilepsia, 22 : 365, 1981

BATTINO D., BOSSI L., CANGER R., COMO M.L., CROCI D., SPINA S.

Monitoring of pregnancy in 59 patients with epilepsy.

Abstract : Epilepsia, 22 : 366, 1981

BATTINO D., AVANZINI G., BOSSI L., CANGER R., COMO M.L., CROCI D., SPINA S.

Monitoring of antiepileptic drug plasma levels during pregnancy and puerperium.

Abstract : Epilepsia, 22 : 372, 1981

BOSSI L., BATTINO D., BOLDI B., CACCAMO M.L., FERRARIS G., LATIS G.O., SIMIONATO L.

Anthropometric data and minor malformations in newborns of epileptic mothers.

Abstract : Epilepsia, 22 : 374, 1981

BOSSI L., BATTINO D., CACCAMO M.L., DE GIAMBATTISTA ., LATIS G.O., OLDRINI A., ROSSI F., SPINA S.

Pharmacokinetics and clinical effects of antiepileptic drugs in newborns of chronically treated epileptic mothers.

Abstract : Epilepsia, 22 : 368, 1981

BOSSI L.

Newborns of epileptic mothers - a review of clinical and pharamcological findings in the perinatal and neonatal period.

BATTINO D., **BOSSI L**., CANGER R., MARGSTAKLER E., MOLTENI B., ROSSI E., SPINAL S.

Coagulation function in newborns treated in utero with antiepileptic drugs.

Abstract: Epilepsia 22: 367, 1981

LE TOUQUET - 1-4 October 1980

Colloque Neuroscience (DGRST, CNRS, INSERM)

MUNARI C., STOFFELS C., **BOSSI** L., TALAIRACH J., LLOYD K.G., ROVEI V., WORMS P., MORSELLI P.L., BANCAUD J.

Aspects neuropharmacologiques et neurochimiques du cortex cérébral chez l'homme épileptique.

Abstracts, pp. 7-8

SANTA MARGHERITA LIGURE - November 1980

Riunione autunnale Società Italiana EEG e Neurofisiologia Clinica

MUNARI C., STOFFELS C., **BOSSI L**., TALAIRACH J., ROVEI V., BANCAUD J., MORSELLI P.L.

Aspetti neurofarmacologici in pazienti con epilessia resistente alla terapia medica

ROME - November 1980

Riunione annuale Sociétà Italiana Neurochirurgia

MUNARI C., TALAIRACH J., **BOSSI L**., STOFFELS C., ROVEI V., BANCAUD J., MORSELLI P.L.

Concentrazioni cerebrali dei farmaci antiepilettici in pazienti con epilessia resistente ai trattamenti farmacologici

1981

PARIS - 8 March 1981

Société d'EEG et de Neurophysiologie Clinique de langue française

BOSSI L., MUNARI C., STOFFELS C., BONIS A., BACIA T., TALAIRACH J., BANCAUD J.

Manifestations somatomotrices dans les crises d'épilepsie d'origine temporale

Abstract: EEG Clin. Neurophysiol., 55: 13, 1983

SERRE-CHEVALIER - 22-29 March 1981 (chairperson)

Méthodologie des essais cliniques en neurologie

BOSSI L.

Intérêt de la détermination des taux plasmatiques des médicaments au cours des essais cliniques.

PARIS - 27-30 April 1981

Fourth International meeting of pharmaceutical physicians

BOSSI L., HENRY J.F., VADROT M.

Methodological problems in the determination and evaluation of adverse events during the phases I, II and III of drug development

MARSEILLE - 4-5 May 1981

Xèmes journées de Méthodologie de la Recherche en Psychiatrie

BOSSI L., MORSELLI P.L.

Intérêt des études pharmacocinétiques et de la surveillance des niveaux plasmatiques des neuroleptiques en psychiatrie.

SEILLAC - 6-9 May 1981

Workshop on Neurotransmitters in epilepsy (WONIEP I):

BOSSI L., ZIVKOVIC B., SCATTON B., MORSELLI P.L., MUNARI C., STOFFELS C, BANCAUD J.

Ventricular CSF concentrations of monoamine metabolites in epileptic patients Abstracts

LLOYD K.G., MUNARI C., BOSSI L., TALAIRACH J., MORSELLI P.L.

Biochemical evidence for the alterations of GABA-mediated synaptic transmission in human epileptic foci

Abstracts

AVIGNON - 11-15 May 1981

Vth International Symposium on Column liquid chromatography SMERDJIAN ROUQUIER L, **BOSSI L.**, SCATTON B.

Concurrent determination of 5-hydroxytryptophan serotonin and 5-hydroxyindoleacetic acid in rat brain and human biological fluids by reversed-phase high performance liquid chromatography with electrochemical detection.

Abstracts.

PARIS - 3 June 1981

Société d'EEG et de Neurophysiologie Clinique de Langue Française

AVANZINI G., BOSSI L., CARENINI L., FRANCESCHETTI S., PARINI C.

Evaluation électro-clinique de l'effet sur les myoclonies non post-anoxiques de substances supposées agir sur les neuromédiateurs.

SANTA FLAVIA (PALERMO) - 18-20 June 1981

Convegno Lega Italiana contro l'Epilessia

BOSSI L.

Epilessia, farmacoresistenza e sistema GABA : dati farmacologici e biochimici tissutali e liquorali nell'uomo.

KYOTO - 13-18 September 1981

International Meeting on EEG and Clinical Neurophysiology

MORSELLI P.L., BOSSI L., MUNARI G.

Should EEG recordings be included in clinical trials of anticonvulsant drugs?

KYOTO - 17-21 September 1981

XIIIth Epilepsy International Symposium:

(chaiperson of session « Neurotransmitters and other substances »)

MUNARI C., STOFFELS C., **BOSSI** L., BRUNET P., BONIS A., BANCAUD J., TALAIRACH J.

Partial seizures with elementary or complex symptomatology: a valid classification for temporal lobe seizures?

Abstracts, p. 61-62

STOFFELS C., MUNARI C., **BOSSI L**., BRUNIE-LOZANO E., BONIS A., BANCAUD J., TALAIRACH J.

Seizures of the anterior cingular gyrus in man: a stereo-EEG study

Abstracts, p. 85-86

BOSSI L., MUNARI C., STOFFELS C., BONIS A., TALAIRACH J., BACIA T., BANCAUD J.

Somatomotor manifestations in temporal lobe seizures Abstract

MORSELLI P.L., MUNARI C., **BOSSI L**., STOFFELS C., BANCAUD J., TALAIRACH J., LLOYD K.G.

Alterations of GABA neuronal biochemistry in surgically resected epileptogenic areas in man Abstracts, p. 88

BOSSI L., MUNARI C., STOFFELS C., BANCAUD J., TALAIRACH J., MORSELLI P.L. Antiepileptic drugs concentrations in brain specimens from therapy resistant epileptic patients

Abstracts, p. 119

MARTINEZ-LAGE M., **BOSSI** L., MORALES G., MARTINEZ-VILA E., POLANOS H. A double-blind cross-over trial of Progabide versus placebo in severe epilepsy Abstract

BOSSI L., ZIVKOVIC B., SCATTON B., DEDEK J., MUNARI C., STOFFELS C., BANCAUD J., TALAIRACH J., MORSELLI P.L.

Ventricular CSF concentrations of NA, DA, HVA, 5-HIAA, cAMP and cGMP in epileptic patients

Abstracts, p. 85-86

LONDON D.R., KANDEEL F., LOIZOU L.A., BUTT W.R., MORSELLI P.L., **BOSSI L.**, VAN LANDEGHEM V.

The endocrine effects of progabide in healthy male volunteers Abstract

MUNARI C., STOFFELS C., **BOSSI L**., BRUNET P., BONIS A., TALAIRACH J., BANCAUD J.

Automatic activities in temporal lobe seizures without involvement of temporal lobe structures

Abstracts, p. 63-64

MILANO - 23-24 October 1981

Idee, proposte e contributi per il piano sanitario regionale : epilessia AVANZINI G., BATTINO D., BINELLI S., **BOSSI L**., BRESCHI F., CACCAMO M.L., CANGER R., CEFALA A., COMO M.L., CROCI D., CUSI C., DE GIAMBATTISTA M., FERRARO G., FRANCESCHETTI S., LATIS G.O., MARINI A., MOISE A., NOLTENI B., PARDI G., PIFAROTTI G., SERENI F., SCHIRO G.P., SIMIONATO L. (Gruppo collaborativo milanese per lo studio dell'epilessia in gravidanza) Gravidanza ed epilessia

HILTON HEAD ISLAND - 6-8 December 1981

Symposium on antiepileptic drugs in newborns, infants, children and adolescents **BOSSI L**.

Fetal effects of anticonvulsants

<u>1982</u>

PERUGIA - May 1982

Réunion conjointe des ligues espagnoles, française et italienne contre l'épilepsie MUNARI C., BONIS A., **BOSSI L**., CHODKIEWICZ J.P., BRUNET P., SZIKLA G., TALAIRACH J., BANCAUD J.

Etude anatomo-electro-clinique de certaines épilepsies post-traumatiques graves chez l'adulte.

JERUSALEM - June 1982

CINP

BATHIEN N., RONDOT P., SEVESTRE P., FOURNIER V., BOSSI L., MORSELLI P.L.

The effect of progabide, a specific GABA-ergic agonist on neuroleptic induced tardive dyskinesia. Results of an open pilot and a double blind placebo trial. Poster.

LONDON - August 1982

XIV Epilepsy International Symposium:

BOSSI L., BIANCHETTI G., CAQUERET H., MORSELLI P.L., GUYOT M., LOISEAU P. Preliminary observations on the possible influence of progabide on the bioavailability of associated AEDs in epileptic patients

Abstracts

BOSSI L., BIANCHETTI G., GUYOT M., CAQUERET H., LOISEAU P., MORSELLI P.L. Preliminary observations on the possible interactions between CBZ and progabide in healthy volunteers

Abstracts

MUNARI G., BRUNET P., CHODKIEWICZ J.P., TALAIRACH J., **BOSSI L.**, BANCAUD J.

Stereo-EEG study of severe post-traumatic epilepsies Abstracts

PHOENIX (ARIZONA) - 10-16 November 1982

Joint annual meeting, American EEG Society, American Epilepsy Society, and WOMAD I (Workshop on the metabolism of antiepileptic drugs) MORSELLI P.L., BURKE J.T., FERRANDEZ B., PADOVANI P., BIANCHETTI G., BOSSI L., GOMENI R., THENOT J.P., THIERCELIN J.P.

Pharmacokinetic profile of progabide in 5 animals species and man Abstract

1983

TORINO - 19 March 1983

Simposio su « Attualità e prospettive in tema di terapia dell'epilessia e monitoraggio dei farmaci

MORSELLI P.L., **BOSSI** L.

Farmaci GABA agonisti come nuovi agenti antiepilettici

SAN ANTONIO (TEXAS) - April 1983

WONIEP II

BOSSI L., MORSELLI P.L.

Antiepileptic efficacy of GABA agonists in man Abstract

9th INTERNATIONAL MEETING OF THE INTERNATIONAL SOCIETY FOR NEUROCHEMISTRY, 1983

LLOYD K.G., MUNARI C., BOSSI L., MORSELLI P.L.

Status of GABA ergic neurons in human epileptic foci, as defined by neurochemistry

ROME - 30 May-2 June 1983

Società Italiana di Neurologia, Società di EEG e Lega contro l'Epilessia **BOSSI L**.

Sistema GABA e farmacoresistenza

WASHINGTON - 26-30 September 1983

15th Epilepsy International Symposium:

WALLACE S.J., BOSSI L.

Response-conditional two-period crossover trial of progabide versus ethosuximide in absence seizures

Abstracts, p 245

WEBER M., VESPIGNANI H., REMY M.L., REGNIER F., BOSSI L.

A double-blind crossover trial of progabide versus placebo in therapy resistant epilepsies Abstracts, p 348

BOSSI L., BEAUSSART M., BENOIT, BROGLIN D., CAMBIER J., CHATEL M.,

DEVILLE M.C., FAVEL P., GEETS, GOAS J.Y., LOISEAU P., LOUETTE

Long term treatment with progabide in severe epileptic patients : preliminary results of a multicenter trial

Abstracts, p 344

MORSELLI P.L., LOISEAU P., MARTINEZ-LAGE M., BOSSI L.

Long term treatment with progabide in resistant epilepsies

Abstracts, p 167

LOISEAU P., COURJON J., KURTZ D., GAREL S., MICHELETTI G., VERCELLETTO P., **BOSSI L**.

Multicenter comparative trial of progabide versus sodium valproate in therapy resistant epilepsies

Abstracts, p 345

LLOYD K.G., MUNARI C., BOSSI L., MORSELLI P.L.

Biochemistry of hyman epileptic brain tissue

Abstracts, p 84

BATTINO D., BINELLI S., **BOSSI L**., CANGER R., COMO M.L., CUSI C., DE GIANBATTISTA M., PARDI G., AVANZINI G.

Monitoring of antiepileptic drugs, estrogen, estriol placental lactogen and progesterone concentrations in pregnant epileptics

Abstracts, p 58

BOSSI L., BATTINO D., CACCAMO M.L., CUSI C., LATIS G., MOISE A., MOLTENI B., BRESCHI F.

Risk of malformations in newborns of epileptic mothers. Updated results of the Milan Collaborative study

Abstracts, p 234

BATTINO D., BINELLI I., CACCAMO M.L., CROCI D., CUSI C., BOSSI L.

Anthropometric data in 100 newborns of epileptic mothers: relationship to antiepileptic drugs Abstracts, p 272

BOSSI L., BATTINO D., BINELLI S., CUSI C., CACCAMO M.L., LATIS G.

Side effects of AEDs in 100 newborns of epileptic mothers-relationship to drug type and blood concentrations

Abstracts, p 274

<u>1984</u>

PARIS - 29 February-2 March 1984 (chief organizer & editor)

Epilepsy and Gaba Receptor agonists: Basic and Therapeutic Research. International Symposium:

LLOYD K.G., **BOSSI L.**, MORSELLI P.L., MUNARI C., ROUGIER M., LOISEAU P. Biochemical evidence for the dysfunction of GABA synapses in human epilepsy

DULAC O., **BOSSI L**., REGNIER F., POULAIN D., BATTIN J., DANDELOT J.B., ATHUIS M.

Long term open trial of progabide in epileptic children

BOSSI L., BEAUSSART M., COURJON J., FOURNIER V., GAREL S., KURTZ D., MARESCAUX C., MEAULLE F., MICHELLETTI G., OROFIAMMA B., VERCELLETTO P., WEISS E., LOISEAU P.

Multicentric study of progabide versus sodium valproate in epilepsy

COQUELIN J.P., KRALL R., **BOSSI L.**, MUSCH B., MORSELLI P.L. Progabide safety

BOSTON - 8-14 April 1984

American Academy of Neurology

DANDELOT J.B., BOSSI L., POULAIN D., MUSCH B., MORSELLI P.L.

Progabide monotherapy in previously untreated epileptic patients

Abstracts: Neurology, Vol 34, Number 3, suppl. 1:6, p 266

LES EMBLIEZ - 15-19 May 1984

GESA XIV (Groupe d'étude Structure-Activité)

BOSSI L.

Agonistes des récepteurs GABA et épilepsie : le profil antiépileptique du progabide chez l'homme

Abstract

FLORENCE - 20-23 June 1984

14th CINP Congress:

BOSSI L.

Progabide in childhood epilepsy

Abstract

LOISEAU P., BOSSI L., MORSELLI P.L.

Clinical experience with GABA agonists

Abstract

FOURNIER V., SEVESTRE P., ZIEGLER M., BATHIEN N., **BOSSI L**., MUSCH B., MORSELLI P.L.,

Results of an open, dose-ranging trial with progabide in neuroleptic induced tardive dyskinesia

Abstract, p. 1027

ZIEGLER M., FOURNIER V., BOSSI L., MUSCH B., RONDOT P., MORSELLI P.L.

The effects of progabide on the « on-off » phenomena of long term levodopa treated parkinsonians: results of a double blind trial of progabide versus placebo Abstract, p. 1063

PARIS - 8 August 1984

GABA et maladies affectives : approche expérimentale et clinique. Symposium International MUSCETTOLA G., CASIELLO M., GIANNINI C., **BOSSI** L.

Open pilot study of progabide in depression

PARIS - 3 December 1984

Réunion de la Ligue Française Contre l'Epilepsie : « Epilepsie et tératogénèse » **BOSSI L**.

Epilepsie et tératogénèse, Synthèse et Conclusion pratique

PARIS - 11-14 December 1984

Congrès International du Traitement du Signal en électrophysiologie expérimentale et clinique du système nerveux central

MUSCH B., BOSSI L.

Predictivity of clinical pharmacology studies

<u>1985</u>

BUENOS AIRES - 14-16 March 1985

International Symposium on Extrapyramidal Diseases

BOSSI L.

GABA and movement disorders

ROME - 18-21 April 1985

3rd European Workshop on Clinical Neuropharmacology:

MUSCH B., BOSSI L., FOURNIER V., MORSELLI P.L.

GABA-agonists in the treatment of human dyskinesia

BOSSI L., MUSCH B., FOURNIER V., PIERROT-DESSEILLIGNY E., BUSSEL B., HELD J.P., MORSELLI P.L.

Antispastic effect of progabide in man

NEW YORK - 9-12 June 1985

VIIIth International Symposium on Parkinson's Disease

ZIEGLER M., FOURNIER V., BOSSI L., MUSCH B., MORSELLI P.L., RONDOT P.

Therapeutic response to progabide in neuroleptic and levodopa dyskinesias

HAMBURG - 6-9 September 1985 (chairperson)

16th Epilepsy International Congress:

MUSCH B., CAMBIER J., LOISEAU P., FOURNIER V., **BOSSI L.**, BEAUSSART M., BENOIT C., CHATEL M., DEVILLE M.C., FAVEL P., FERRIERE G., GEETS W., GOAS J.Y., KULAKOWSKI S., LOUETTE N., MARTINEZ-LAGE M., REMY C.

Open long term multicenter trial with progabide in epileptic patients

DULAC O., BOSSI L., ARTHUIS M.

Long term open trial of progabide in epileptic children

BOSSI L., DANDELOT J.B., POULAIN D., MORSELLI P.L.

Progabide monotherapy in previously untreated epileptic patients

PESTRE M., BOSSI L., LOISEAU P.

Acute effects of single dose administration of SL 78 424 on human photosensitivity

BOSSI L., POULAIN D.

Progabide safety after massive overdose in 4 subjects

BOSSI L., MORSELLI P.L.

Fetal effects of progabide

MORSELLI P.L., BENASSI E., BESIO G., BIANCHETTI G., MUSCH B., **BOSSI L.**, LOEB C.

Blood levels of progabide (PGB) and its active metabolite (PGA) in epileptic patients: relationship to the therapeutic outcome

PALMINTERI R., L'HERITIER C., BOSSI L.

Progabide and liver function tests

SOVERATO (CATANZARO) - 17-19 September 1985

Third Workshop on neurotransmitters in epilepsy (WONIEP)

BOSSI L., MORSELLI P.L.

Antiepileptic efficacy of GABA receptor agonists

VILLARD DE LANS (GRENOBLE) - 9-11 October 1985

BOSSI L., BRUNOD R., FOURNIER V., MORSELLI P.L., MUSCH B., RONDOT P., SEVESTRE P., ZIEGLER M.

Neurotransmitter interactions in the basal ganglia

Abstract

HILTON HEAD ISLAND - 18-19 November 1985

Workshop on problems in clinical development of antiepileptic drugs **BOSSI L**.

Design of clinical trials in naive patients

<u>1986</u>

PAMPLONA - 10-13 June 1986 (Member of the International Advisory Board) 4th European Workshop on Clinical Neuropharmacology

1987

WASHINGTON - 30 May-2 June 1987

Regulatory Affairs Professionals Society, 11th International Meeting **BOSSI L**.

Implementation and monitoring of clinical trials in Europe

1990

MADRID - 25-27 January 1990

International Symposium

Ramon y Cajal - past, present and future

BOSSI L.

Three key-words for the next decade

PARIS - 12 June 1990

La Cité des Sciences, Colloque Science, Culture, Institutions

BOSSI L.

Science, Culture, Institutions

ROME - 10-14 July 1990 (poster)

European Conference on Parkinson's Disease and Extrapyramidal Disorders

BOSSI L., GUILLOU G.B., BIANCHETTI A., LEFEVRE A., VIDAILLET M., BONNET A.M., GROUIN J.M., RAKOTONDRAINIBE S., MEYRIGNAC Ch.

Phosphatidylserine as an add-on therapy in L-Dopa treated parkinsonian patients

PRAGLIA ABBEY (PADOVA) - October 1990 (invited participant)

International School of Neuroscience, 2nd course, Developmental neurobiology

1991

BORDEAUX - 26-27 April 1991

Functional recovery in the central nervous system

BOSSI L.

Degeneration and regeneration of the nervous system: new pharmacological approaches

<u>1992</u>

LAUSANNE (SWITZERLAND) - 25-27 June 1992

Second European Stroke Conference

ORGOGOZO J.M., CAUSSANEL J.P., WOIMANT F., GROUIN J.M., GUILLOU G.B., **BOSSI L**.

FOR THE I.S.G. STUDY GROUP

Outcome of MCA infarction with severe brain oedema. A prospective study.

YOKOHAMA (JAPAN) - 26-31 July 1992

Vth World Conference on Clinical Pharmacology and Therapeutics

GUILLOU G.B., BIANCHETTI A., GUILLAUME M., DOUIN M.J., THEBAULT J.J., **BOSSI L**.

Pharmacokinetics of two doses of CRONASSIAL (40 and 100 mg) after single and repeated I.M. administration to healthy volunteers

BIANCHETTI A., GUILLOU G.B., GUILLAUME M., DOUIN M.J., MIGNOT A., **BOSSI L**.

Pharmacokinetics of SYGEN (100 mg) after single I.V., I.M., S.C. administration to healthy volunteers

IBIZA (SPAIN) - 15-17 October 1992 (invited speaker)

Valencian Society of Neurology

BOSSI L.

Utilidad del GM1 en patologia vascular cerebral

1993

NEW-YORK - 25 April-1st May 1993

American Academy of Neurology, 45th Annual Meeting:

BOSSI L., GROUIN J.M., GUILLOU G.B., PRIVAT A., TADIE M.

New approaches to the design of clinical trials in acute spinal cord injury

Abstract: Neurology

BOSSI L.

Cesare Lombroso: the born criminal and epilepsy

Abstract: Neurology

VANCOUVER - 5-10 September 1993 (poster)

XVth World Congress of Neurology

BOSSI L.

An iconographic approach to the clinical picture of hysteria in the work of J.M. Charcot and P. Richer

Abstract

1998

INGOLSTADT, (Deutsches Medizinhistorisches Museum), 14 February 1998 (invited speaker)

Münchner Medizinische Wochenschrift-Arzneimittelpreis

L. BOSSI

Lange Tradition und wichtige Zukunftsoption bei Sanofi

MARNES LA COQUETTE, November 3, 1998 (invited speaker)

Les neuropathies autoimmunes

L. BOSSI

Perspectives thérapeutiques des neuropathies périphériques

PARIS, 5-7 November 1998 (invited speaker)

Alzheimer's disease: the therapeutic era

L.BOSSI, Disease-modifying treatment for Alzheimer's disease: the neurotrophic approach.

Abstract: Alzheimer's reports, Vol.1, Suppl.1, November 1998, S29

1999

MONTPELLIER, 17 March 1999 (invited speaker)

La semaine du cerveau

L. BOSSI

Stratégies de recherche de nouveaux médicaments

2000

PARIS, 4 October 2000 (invited speaker)

Les effets secondaires des anticancéreux

L. BOSSI

Neurotoxicité des dérivés du platine

2001

TILLBURG (Hollande) 4 February 2001 (invited speaker)

Nexus conference 2001

The quest of life: Love and death

L.BOSSI

The future of death

2002

BUDAPEST (Hungary), March 22-23, 2002 (invited speaker)

Eloxatin international meeting

L. BOSSI

Managing neurosensory symptoms